Appendices

Appendix 1: Detailed Background and Rationale for the MyTEMP Trial

Maintenance hemodialysis provides a life-saving treatment for persons whose kidneys have permanently failed (approximately 3 million worldwide and 23,000 in Canada).[1,2] However, over 400,000 individuals worldwide (2,500 persons in Canada) are admitted to hospital- or die from a major cardiovascular-related event each year.[3–5]

In most hemodialysis centers, the default dialysate temperature setting is in the range of 36.5 °C to 37.0 °C. Lowering the dialysate temperature below a patient's core body temperature (such a value of 35 °C to 36 °C) is a promising intervention that has the potential to reduce the risk of cardiovascular-related mortality and major adverse cardiovascular events.[6–8] Lowering the dialysate temperature stabilizes intradialytic blood pressure and decreases the risk of experiencing hypotensive events during hemodialysis treatments[9] – experiencing frequent hypotensive events during hemodialysis is associated with a greater risk of all-cause mortality and cardiovascular events.[10]

1.1 Physiology of intradialytic hypotension

There is evidence showing hemodialysis itself injures the heart, brain, and other vital organs through repeated episodes of intradialytic hypotension and subclinical ischemia.[10–17] Most intradialytic hypotensive events are attributed to the ultrafiltration that occurs during dialysis and an inadequate cardiovascular compensation to replace the loss in blood volume.[18] When fluid is removed from the body during hemodialysis, systolic blood pressure often drops by an average of 20 mmHg to 30 mmHg and diastolic blood pressure drops by 7 mmHg to 10 mmHg.[10,19] The normal physiological response to reductions in blood volume for healthy individuals is an increase of peripheral vascular resistance, an increase in the heart stroke volume, and/or a faster heart rate. Healthy individuals can tolerate up to a 20% loss in circulating blood volume before they experience hypotension.[20,21] However, many patients

on hemodialysis are unable to mount the response seen in healthy persons, and hypotension occurs with a smaller decline in blood volume.[22] This inability to mount a normal response has been partly attributed to impairment in myocardial contractile reserve due to cardiomyopathy.[23,24] Beyond ultrafiltration, there are multiple patient and dialysis-associated factors that contribute to intra-dialytic hypotension including poor sympathetic responsiveness,[25] poor cardiac function,[26,27] older age (possibly related to increasing comorbid conditions),[28] medication use (e.g. use of anti-hypertensive agents),[29] body heating,[30–32] release of vasodilator agents,[33,34] and osmolar and electrolyte changes.[35–38]

Large drops (greater than 20 mmHg) in blood pressure complicate up to 50% of hemodialysis sessions.[22] Intradialytic hypotension increases the risk of coronary hypoperfusion that can lead to myocardial stunning,[39,40] which is associated with left ventricular dysfunction.[13,15,41–43] When the left ventricle starts losing its ability to pump blood, the heart's compensatory mechanisms further loses the ability to compensate for the loss in blood volume during ultrafiltration – possibly leading to further hypotensive events and the damage of vital organs. Over time, the cumulative effect of intra-dialytic hypotensive events – each time resulting in small ischemic insults – may lead to a higher risk of major adverse cardiovascular events and cardiovascular-related death.[12,19,44]

1.2 Physiologic effects of reduced dialysate temperature

One strategy to help stabilize blood pressure during hemodialysis is to reduce the temperature of the dialysate. A cooler dialysate temperature increases peripheral vascular resistance, improves cardiac function, and alters the level of vasoactive peptides — all which may stabilize blood pressure.[30,32,45–50] [10] The measures used to described blood pressure differences between cooler dialysate temperature (≤35.5 °C) vs. a standard dialysate temperature (≥36.0 °C) in prior individual level RCTs has not been consistent; with some reporting mean intra-dialytic systolic blood pressure, nadir intra-dialytic systolic

blood pressure, and pre- and post-dialysis blood pressure. Nevertheless, these studies reported with a cooler compared to standard dialysate temperature there was a: (i) higher nadir systolic blood pressure; (ii) a smaller drop in post-dialysis from pre-dialysis blood pressure; and (3) a smaller drop in nadir intra-dialytic from pre-dialysis blood pressure - (***eTable 1***).[40,47,51–58]

Compared to a dialysate temperature of 37 °C, personalized dialysate temperature (0.5 °C below pre-dialysis core body temperature) over a 12-month period reduced injury to both the brain and heart. In the brain, temperature-reduced hemodialysis protected patients against white matter changes as a result of less injuries to cerebral vascular beds.[13] In the heart, temperature-reduced hemodialysis resulted in positive (but not statistically significant) changes in resting ejection fraction, however, there was a statistically significant reductions in both left ventricular mass and left ventricular end-diastolic volumes, and aortic distensibility was preserved.[15] A cardio- and neuro-protective effect of cooler dialysate temperature may operate through several mechanisms beyond stabilizing blood pressure and reducing the risk of intra-dialytic hypotension. Other mechanisms may include: lowering cell metabolism, reducing the likelihood of experiencing calcium overload, reducing inflammatory factors, and increasing anti-apoptotic factors.[59–62]

1.3 Clinical effects of reduced dialysate temperature

We conducted a systematic review and meta-analysis that identified 26 randomized controlled trials (total 484 patients) investigating the effect of cooler dialysate temperature compared to a standard temperature. Most of the trials enrolled less than 30 patients and only three trials followed patients for longer than six sessions.[47,54,63] In this review, temperature-reduced hemodialysis (34-35.5 °C) compared to control (where in different jurisdictions ranged from 36 °C to 38.5 °C), reduced the rate of intra-dialytic hypotension by 70% (95% CI: 49% to 89%). The intra-dialytic mean arterial pressure increased by

an average of 12 mmHg (95% CI: 8 to 16 mmHg) for temperature-reduced hemodialysis compared to standard temperature hemodialysis, and several studies reported a smaller reduction in average intra-dialytic nadir and post-dialysis systolic blood pressure compared with pre-dialysis blood pressure reading.[9,51–53] The of risk adverse events was not statistically different compared with standard dialysate temperature. However, these results should be interpreted with caution as the methodological quality of the 26 trials was rated as low to very low using GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation criteria).[64,65]

Observational studies have reported inconsistent results with regards to the effect of temperature-reduced hemodialysis on mortality in comparison to the control temperature. Hsu *et al.*[66] found the use of cooler dialysate temperature (<35.5 °C) was associated with a 35% lower risk of cardiac mortality and 25% lower risk of all-cause mortality compared to patients that used a dialysate temperature between 35.5 and 37 °C. Similarly, data on 8807 patients from 232 hemodialysis facilities across 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 4 (2009-2012) showed cool dialysate was associated with a 24% reduction in the risk of cardiovascular-related mortality (HR=0.76; 99% CI: 58%-98%), but was not associated with an altered risk of all-cause hospitalization (HR=1.12; 99% CI 0.98-1.27), all-cause mortality (HR=1.04; 99% CI 0.87-1.24), or major cardiovascular events (HR=0.94; 99% CI 0.80-1.11).[67] In a study comparing outcomes of cool dialysate at a temperature of 36 °C (n=313 patients) with matched-control patients with a dialysate temperature of 37 °C (n=1565), Gray et al.[68] found no difference in the risk of hospitalization (incidence rate ratio [IRR]=1.10; 95% CI 0.94-1.29) or all-cause mortality (IRR=1.09; 95% CI 0.77-1.53).

Some have suggested that a cooler dialysate temperature may reduce uremic toxin removal compared to a warmer dialysate temperature; however, this was not supported in our systematic review above when all prior studies were considered.[9] As well, other studies investigating the effect of a cooler dialysate on urea removal found that urea-based dialysis adequacy is largely unaffected by dialysate

temperature.[9,57,69,70] However, others have suggested urea removal is not a good marker for toxin removal because of its small size and generally negligible inter-compartmental resistance.[71] There is an ongoing clinical study of 14 patients that aims to compare toxin removal for patients on cool and warm dialysate for both small and large-sized toxins.[71] Of note, if a cooler dialysis temperature enables a patient to receive more dialysis or more ultrafiltration than they would otherwise receive with a warmer dialysis temperature (e.g. dialysis treatments are stopped early for reasons of intra-dialytic hypotension or cramping) this would increase uremic toxin removal.

1.4 What is the dialysate temperature used in current practice?

Currently, the dialysate temperature used in most centres in Canada and the United States ranges from 36.5 °C to 36.7 °C (97.7°F to 98.1°F). In preparation for the MyTEMP trial, we collected data on the prescribed dialysate temperature and patients' pre-dialysis body temperatures for 12,012 hemodialysis sessions across 68 unique hemodialysis centres in Ontario over a six-month period (September 2016 to March 2017). Results are reported as the median (25^{th}, 75^{th} percentile). We confirmed the delivered dialysis temperature during this period was fixed for each dialysis session except for 5 of the 68 hemodialysis centres that used blood temperature monitoring. The prescribed dialysate temperature was 36.5 °C or 97.7 °F (36 °C [96.8 °F], 36.5 °C [97.7 °F]). The pre-dialysis body temperature was 36.3 °C or 97.3 °F (35.9 °C [96.6 °F], 36.6 °C [97.9 °F]) and 59% of hemodialysis sessions started with a pre-dialysis body temperature (measured using oral or tympanic instruments) less than 36.5 °C (97.7 °F). The difference between the pre-dialysis body temperature and prescribed dialysate temperature was 0.0 °C (0.3 °C lower, 0.4 °C higher than body temperature).

In the United States, it has been estimated that the average delivered dialysate temperature is 36.7 °C (98.1 ºF).[72] The prescribed dialysate temperature of 36.5 °C (97.7 °F) used by most nephrologists comes

from clinical tradition rather than empirical evidence; with the historic rationale that dialysate temperature should be similar to typical body temperature.

1.5 How is the dialysate temperature set and maintained?

There are several types of hemodialysis mechanisms that control the dialysate temperature. These methods include fixed, programmed, isothermic, thermoneutral, and negative energy hemodialysis prescriptions.[6] The fixed method uses a single non-variable dialysate temperature that is prescribed throughout a patient's hemodialysis session. The latter four methods use blood temperature monitoring to make constant adjustments to the dialysate temperature during hemodialysis in response to the measured body temperature.

The fixed dialysate temperature prescription is currently the most common prescription method used in Ontario and likely worldwide. All hemodialysis machines have the mechanisms and software to achieve a fixed dialysis temperature, which makes this method of temperature control popular. To set a fixed dialysate temperature, a physician or nurse practitioner prescribes a specific temperature for a patient's hemodialysis treatment, and a dialysis nurse programs the fixed temperature into the hemodialysis machine. The nurse monitors the patient during the treatment, and some have the authority to alter the dialysate temperature during the treatment according to the patient's symptoms (e.g. temperature may be adjusted as per patient's condition).

In Ontario, the most commonly used dialysis machines are the Fresenius 5008 and the Baxter Artis. Purified water enters the machine through an inlet valve at a temperature between 5 °C and 30 °C. Then, the purified water passes through a passive heat exchanger where the spent dialysate that passed through the dialyzer passively heats the incoming purified water entering the hemodialysis machine. The purified water is then further heated by a heating element at a power correlated to the fixed

dialysate temperature. The heated water is combined with bicarbonate and acid to form the base of the dialysate.

A temperature sensor measures the dialysate temperature to determine if it is equivalent to the programmed dialysate temperature. The communication between the dialysate temperature sensor and the heating element is in a constant feedback loop throughout the hemodialysis session to maintain the programmed dialysate temperature. The temperature sensor in the above-mentioned machines measures the temperature of the water leaving the heater assembly and controls the heater to ensure that the: (a) temperature is within operating range; (b) maximum temperature deviation is within acceptable range; and (c) response time is within acceptable range. The Fresenius 5008 and Baxter Artis machines have different temperature circuit specification as shown in **eTable 2**.

Continuous monitoring of the dialysate fluid temperature is monitored by the protection system throughout the treatment session (**eFigure 1**). If the dialysate temperature cannot be maintained within the allowable operating and accuracy range (as specified in **eTable 2**) due to a failure in the temperature circuit, for patient safety an alarm is activated to warn the nurse and the bypass function is activated for the patient's blood to bypass the dialyzer.

1.6 How does body temperature change in response to the dialysate temperature?

In general, human body temperature is maintained within a narrow range. Several studies show that during conventional hemodialysis with the dialysate temperature set at 36.5 to 37 °C, temperature can increase by 0.1 to 0.9 °C at various parts of the body, including the arterial fistula line, oral cavity, and skin surface.[73] In the skin, decreases in body temperature as small as 0.3 °C can alter vascular tone; whereas, reductions in skin temperature of 0.8 °C associates with symptoms of shivering.[73] Using historic data from 4407 sessions, **eTable 3** shows as the dialysate temperature becomes cooler, the

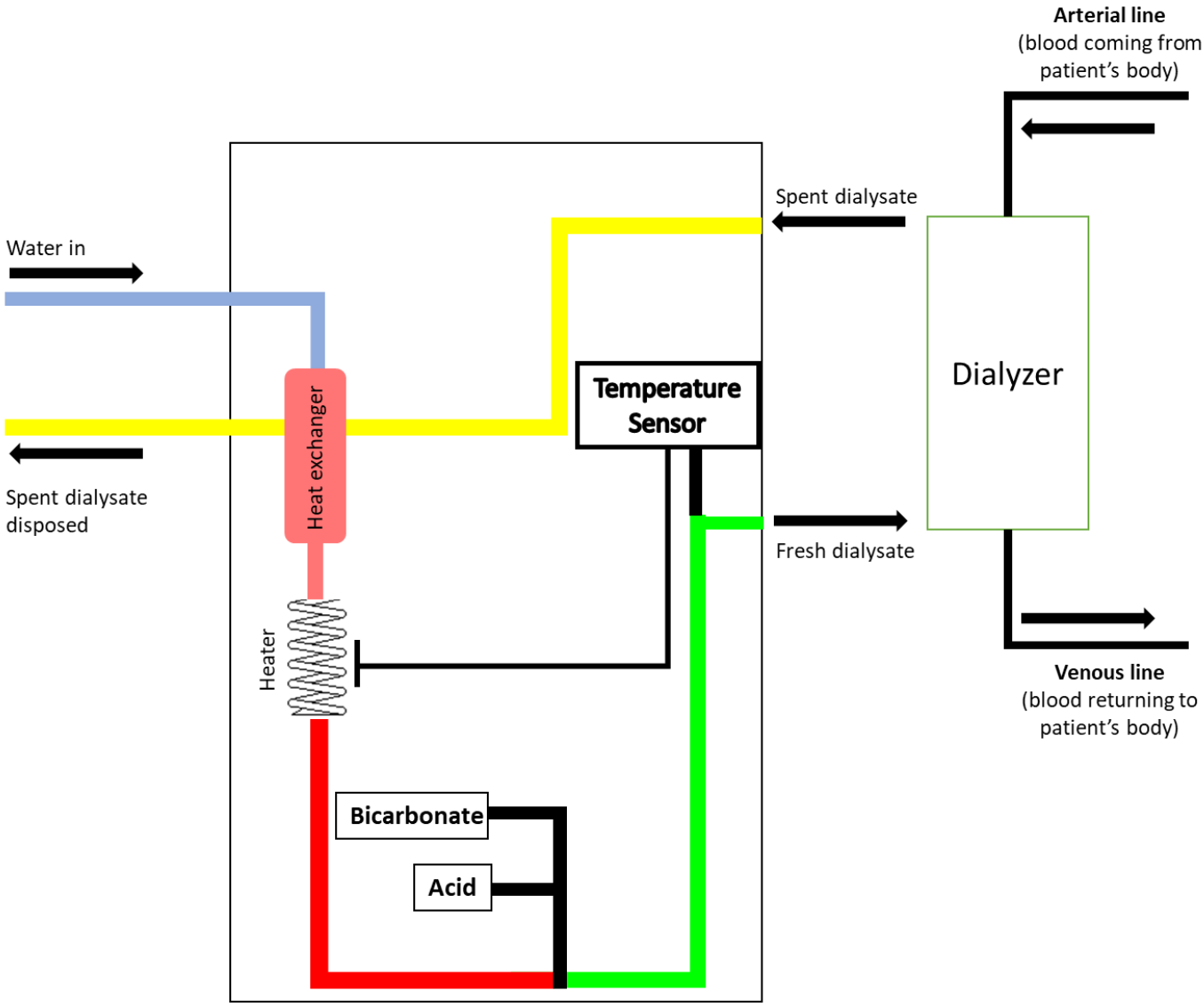
post-hemodialysis body temperature decreases after accounting for pre-hemodialysis body temperature.

Effects of temperature-reduced dialysis on patient symptoms. Some patients may experience feeling cold when using temperature-reduced hemodialysis.[9,40] In MyTEMP, we are *personalizing* the dialysate temperature for each patient, rather than using a single fixed cool temperature for all patients. In turn, this may improve tolerability for more patients. In a previous study, most patients using fixed temperature-reduced hemodialysis of 35 °C reported positive views of their experience and wanted to continue using the cooler temperature after study completion.[7,74] Patients also reported perceived benefits such as having more energy, better cognition, less post-hemodialysis fatigue, and a quicker time to recovery after their hemodialysis session.[9,74–76]

1.7 The need for large multi-centre trials of temperature-reduced hemodialysis

Many in the nephrology community have called for large-scale testing of temperature reduced dialysis.[8,9,77] Current trials of temperature-reduced hemodialysis registered on clinicaltrials.gov have fewer than 150 patients and none of the prior or current studies investigate major outcomes when a hemodialysis facility changes its protocol from a standard hemodialysis dialysate temperature of ≥36.5 °C to personalized temperature-reduced hemodialysis. To inform clinical practice change, we need evidence from at least one large, pragmatic, high-quality, multi-centre randomized controlled trial (that is generalizable to most hemodialysis centres) and has adequate statistical power to detect a meaningful change in the rates of major outcomes.

eFigure 1: Purified water (light blue) enters the hemodialysis machine where it passes through a passive heat exchanger. Spent dialysate (yellow) after leaving the dialyzer passively heats the purified water entering the hemodialysis machine (light red). The purified water is further heated by a heating element at a power that will raise the fresh dialysate to the desired programmed temperature (red). The heated water is combined with bicarbonate and acid to form the base of dialysate (green). A temperature sensor is used to measure the dialysate temperature to determine if it is equivalent to the programmed dialysate temperature. The temperature sensor will communicate with the heating element (by switching on or off) to achieve the programmed temperature.



eTable 1: Summary of systolic blood pressure measures in previous randomized controlled trials

Reference	N Patients	Dialysate temperature	Blood Pressure Measures ¥	
			Cooler dialysate temperature	Standard dialysate temperature
Beerenhout 2004 [51]	12	Fixed temperature 35.5 °C; duration: one session Vs Fixed temperature 36.0 °C; duration: one session	Change in SBP: -6 ± 2 mmHg	Change in SBP: -0.8 ± 22.7 mmHg
Beerenhout 2004 [52]	12	BTM (mean dialysate temperature 35.2 °C); duration: one session Vs Fixed temperature 37.5 °C; duration: one session	SBP pre-dialysis: 146 ± 5 mmHg SBP post-dialysis: 140 ± 6 mmHg	SBP pre-dialysis: 150 ± 5 mmHg SBP post-dialysis: 132 ± 4 mmHg
Chesterton 2009 [53]	10	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Percent change in SBP: 2.71% above baseline ± 0.97%	Percent change SBP: 7.54% below baseline ± 1.92%
Cruz 1999 [54]	19	Fixed temperature 35.5 °C; duration: nine sessions	SBP pre-dialysis: 132 ± 3.3 mmHg Nadir SBP: 103 ± 2.9 mmHg	SBP pre-dialysis: 132.7 ± 3.4 mmHg Nadir SBP: 90.6 ± 2.5 mmHg

		Vs Fixed temperature 37 °C; duration: nine sessions	SBP post-dialysis: 118 ± 3.5 mmHg	SBP post-dialysis: 109.0 ± 2.1 mmHg
Maggiore 2002 [47]	95	BTM isothermic; duration: 12 sessions on average Vs BTM thermoneutral; duration: 12 sessions on average	Change in SBP between post- and pre-dialysis readings: -14 ± 17 mmHg * Post-dialysis SBP was 14 mmHg below pre-dialysis SBP	Change in SBP between post- and pre-dialysis readings: -21 ± 16 mmHg * Post-dialysis SBP was 21 mmHg below pre-dialysis SBP
Parker 2007 [55]	7	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Intra-dialytic SBP: 137 ± 11.4 mmHg	Intra-dialytic SBP: 130.7 ± 11.4 mmHg
Selby 2006 [40]	10	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Intra-dialytic SBP: 159 ± 14 mmHg	Intra-dialytic SBP: 142 ± 17 mmHg

van der Sande 1999 [56]	9	Fixed temperature 35.5 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	SBP pre-dialysis: 130 ± 22 mmHg Max ↓ in SBP: 21.8 ± 26.1 mmHg SBP post-dialysis: 132 ± 21 mmHg	SBP pre-dialysis: 144 ± 26 mmHg Max ↓ in SBP: 43 ± 20.6 mmHg SBP post-dialysis: 117 ± 26 mmHg
Kaufman 1998 [57]	17	BTM isothermic; BTM cooling 0.5 °C below body temperature; duration: 1.5 sessions on average Vs BTM thermoneutral; duration: 1.5 sessions on average	SBP pre-dialysis: 159 ± 35 mmHg Nadir SBP: 113 ± 30 mmHg SBP post-dialysis: 127 ± 39 mmHg	SBP pre-dialysis: 151 ± 27 mmHg Nadir SBP: 104 ± 27 mmHg SBP post-dialysis: 122 ± 28 mmHg
Zitt 2008 [58]	17	Fixed temperature 35 °C; duration: not clear Vs Fixed temperature 37 °C; duration: not clear	SBP pre-dialysis: 127 ± 6.4 mmHg SBP post-dialysis: 134 ± 3.9 mmHg	SBP pre-dialysis: 126 ± 4.6 mmHg SBP post-dialysis: 127 ± 2.1 mmHg

SBP=systolic blood pressure (mean ± standard deviation); Max ↓ in SBP: Maximum drop in intradialytic SBP (difference between pre-dialysis and nadir intra-dialytic SBP); Intra-dialytic SBP: Mean intradialytic SBP during the hemodialysis session;

¥ Information presented is Mean ± SD

eTable 2: Default temperature circuit specification for the Fresenius 5008 and Baxter Artis hemodialysis machines.

Machine	**Fresenius 5008**	**Baxter Artis**
Dialysate temperature range	+34 °C to +39 °C	+35 °C to +39.5 °C
Accuracy[**]	+0.2 °C/-0.5 °C of the set value	+0.5 °C/-1.8 °C of the set value
Resolution[++]	0.5 °C	0.5 °C (0.1 °C is possible)

[**]Accuracy of the delivered dialysate temperature compared to the programmed dialysate temperature.

[++] The resolution (increments) at which the dialysate temperature can be programmed on the machine.

eTable 3: Change in body temperature by different levels of dialysate temperature using historic data from 4407 sessions. Patient body temperatures were measured using tympanic thermometers.

Dialysate is:	Dialysate Temperature	Arrival Temperature (Pre-dialysis)	Departure Temperature (Post-dialysis)	Change in Body Temperature**
At least 1 °C above body temperature	37 (36.5, 37.5)	35.8 (35.5, 35.9)	36.3 (36.1, 36.5)	0.7 (0.4, 1)
0.5 to 0.99 °C above body temperature	36.5 (36.5, 36.5)	36 (36, 36)	36.3 (36.1, 36.5)	0.3 (0.1, 0.6)
0.01 to 0.49 °C above body temperature	36.5 (36.5, 36.5)	36.3 (36.2, 36.4)	36.4 (36.3, 36.6)	0.2 (0, 0.4)
Equal to body temperature	36.5 (36.5, 36.5)	36.5 (36.5, 36.5)	36.5 (36.3, 36.7)	0.1 (-0.1, 0.2)
0.01 to 0.49 °C below body temperature	36.5 (36, 36.5)	36.6 (36.4, 36.7)	36.6 (36.4, 36.7)	0 (-0.2, 0.2)
0.5 to 0.99 °C below body temperature	36 (36, 36)	36.6 (36.6, 36.8)	36.5 (36.4, 36.7)	-0.1 (-0.3, 0.1)
At least 1 °C below temperature	35.5 (35.5, 36)	36.7 (36.6, 37)	36.5 (36.4, 36.7)	-0.2 (-0.5, 0)

** Change in Body Temperature refers to the difference in each patients' arrival from departure temperature. A positive number means the departure temperature greater (i.e., warmer) than the arrival temperature.

Columns are presented as median (25^{th}, 75^{th} percentile).

To convert from °C to °F, use the formula: (Temperature °C × 1.8) + 32;

Appendix 2: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have dialysis machines able to change by increments of 0.1°C

Patient Temperature* (°C)	**Dialysate Temperature (°C)**
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.5
37.3	36.5
37.2	36.5
37.1	36.5
37	36.5
36.9	36.4
36.8	36.3
36.7	36.2
36.6	36.1
36.5	36
36.4	35.9
36.3	35.8
36.2	35.7
36.1	35.6
36 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 3: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have hemodialysis machines able to change by increments of 0.5 °C

Patient Temperature* (°C)	**Dialysate Temperature (°C)**
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.5
37.3	36.5
37.2	36.5
37.1	36.5
37	36.5
36.9	36
36.8	36
36.7	36
36.6	36
36.5	36
36.4	35.5
36.3	35.5
36.2	35.5
36.1	35.5
36 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 4: Sampling accuracy for overall centre adherence

For eight centres, we had access to the full patient data on adherence to the allocated temperature protocol (5 centres in the control and 3 centres in the intervention arm). We sampled 15 patients 1000 times from each centre and compared the sampled adherence to the true adherence for all patients within the respective centre. The sampled adherence was within 10% of the true adherence approximately 50% to 90% of the time. The sampled adherence was within 20% of the true adherence over 80% of the time for all centres. We found as the true centre adherence increased towards 100%, so did the accuracy of our estimated sample adherence.

Appendix 5:

MyTEMP met the necessary criteria for alteration to the patient consent process as outlined in the TCPS-2 Statement: (i) the research poses a clear benefit to society and was unlikely to adversely affect patient welfare; (ii) the intervention was considered to be of minimal risk to patients (similar to a quality-control measure that could be implemented by a dialysis centre director); (iii) an informed consent model is impossible and impracticable given our research design and resources (e.g. a source of bias if patients in a hemodialysis centre randomly allocated to personalized temperature are less likely to consent to trial participation [a change compared to their historic dialysate prescription] compared to patients in a hemodialysis centre randomly allocated to control arm [where there is no change from what they have historically received]); and (iv) there is a plan to provide a debriefing which also offers patients the possibility of refusing the intervention.[78]

Appendix 6: Common data sources used for population-based studies

Database (Source)	Description	Key Data Variables
Health Services		
Discharge Abstract Database (CIHI)	Hospital discharge abstracts for acute, chronic and rehabilitative care (1988 onward)	Diagnoses; Procedures; Comorbidities; Length of Stay
National Ambulatory Care Reporting System (CIHI)	ED visits, same day surgery, outpatient clinics (e.g., dialysis, cancer clinics) (2002 onward)	Reason for visit; Triage level; Interventions; Mode of arrival
Ontario Drug Benefit Database (MOHLTC)	Claims for prescribed drugs covered by the Ontario Drug Formulary for adults aged 65+ and those receiving social assistance (1990 onward)	Drug ID number; Drug quantity; Cost
Ontario Health Insurance Plan (MOHLTC)	Reimbursement claims made by fee-for-service physicians and community-based labs (1991 onward)	Service provided; Diagnosis codes; Fee paid; Physician specialty
	Registry	
Canadian Organ Replacement Register (CIHI)	Collects and records the incidence, prevalence, treatment changes, and outcomes of all chronic dialysis and solid organ transplant patients in Canada. Data is collected by voluntary completion of survey forms for each patient at dialysis initiation and at yearly follow-up (2001 onward)	Hemodialysis start; vascular access use; nephrology referral; comorbid and baseline conditions
Ontario Renal Reporting System	Collects and records the incidence, prevalence, treatment changes, and outcomes of all chronic dialysis and solid organ transplant patients in Canada. Data is collected is mandated by the Ontario Renal Network for each patient at dialysis initiation and at yearly follow-up (2010 onward)	Hemodialysis start; vascular access use; nephrology referral; comorbid and baseline conditions
Population and Demographics		
Registered Persons Database (MOHLTC)	Basic demographic information about all Ontarians that ever had an Ontario Health Card Number. (1990 onward)	Date of birth; Date of death; Sex; Geographic information

Office of the Registrar General- Deaths (ORGD)	ORGD is an annual dataset containing information on all deaths registered in Ontario starting on January 1st, 1990.	Information on cause **Note**: Information on cause of death lags other variables by ~2 years.
Care Providers		
ICES Physicians Database	This data set contains yearly information about all physicians in Ontario (1992 onward)	Annual demographics; Specialization; Workload
Laboratory Datasets		
Ontario Laboratories Information System (pending linkage)	OLIS is a cornerstone information system that connects hospitals, community laboratories, public health laboratories and practitioners to facilitate the secure electronic exchange of laboratory test orders and results. ICES has signed and currently executing a Data Sharing Agreement to link Ontario-wide laboratory results to the Ontario-wide data holdings housed at ICES.	Creatinine levels, lipid panels, urine protein Outpatient, emergency room and inpatient values.

MOHTC: Ministry of Health and Long-term Care, CIHI – Canadian Institutes for Health Information

Appendix 7: List of 78 variables baseline variables

Medical history of the following		**Databases**
Demographic		
Age		RPDB
Sex		RPDB
Race (includes information about aboriginals)		ORRS
Rural living		RPDB
Socioeconomic status		RPDB
Primary Cause of ESRD		
Diabetes		ORRS
Drug Induced		ORRS
GN/Autoimmune disease		ORRS
Polycystic Kidney Disease		ORRS
Renal Vascular Disease		ORRS
Other		ORRS
Comorbid Factors		
Arrhythmia		OHIP/CIHI-DAD
Amputation		CIHI-DAD
Alcoholism		CIHI-DAD
Atrial Fibrillation/Flutter		CIHI-DAD
CABG/PCI		ORRS / CIHI-DAD/OHIP
Charlson Comorbidity Score		CIHI-DAD
Coronary Artery Disease (with angina)		ORRS/ CIHI-DAD/OHIP
Crash start with AKI		CIHI-DAD
Dementia		ORRS /CIHI-DAD/OHIP
Depression*		CIHI/ODB/OHIP
Diabetes mellitus		ORRS/CIHI-DAD/OHIP
Fracture		CIHI-DAD/OHIP
Heart failure ++		CIHI-DAD
Hemorrhage		OHIP/CIHI-DAD
Hypertension		ORRS/ CIHI-DAD/OHIP
Hypotension		CIHI-DAD
Ischemic Stroke ++		CIHI-DAD
Liver Disease		ORRS/ CIHI-DAD/OHIP

Lung disease (COPD)		ORRS/ CIHI-DAD/OHIP
Malignancy		ORRS /CIHI-DAD/OHIP
Myocardial infarction ++		ORRS/ CIHI-DAD
Other serious illness that would shorten life expectancy less than 5 years		ORRS
Peripheral vascular disease		ORRS/ CIHI-DAD/OHIP
Smoking		ORRS
Stroke/Transient ischemic attack		ORRS/CIHI-DAD
Subarachnoid Hemorrhage		CIHI-DAD
Syncope		CIHI-DAD
Drugs (for 65+ years)		
ACE Inhibitors		ODB
ARB		ODB
Anti-depressants		ODB
Anti-Psychotics		ODB
Benzodiazepine		ODB
Beta-Blockers		ODB
Healthcare Utilization		
Long term care facility utilization		ODB/OHIP/CCRS
Number of nephrology consults in the last 12 months		OHIP
Number of Family Doctor consults in the last 12 months		OHIP
Number of Hospitalizations in last 12 months		CIHII-DAD
Number of Visits to Emergency Department in last 12 months		NACRS
Total Healthcare Costs in last 12 months		Various sources at ICES [79]
Lab Data (Last measured)		
Hemoglobin		ORRS/OLIS
Urea		ORRS/OLIS
eGFR		ORRS/OLIS
Serum Albumin		ORRS/OLIS
Procedures / Monitoring		
Carotid endarterectomy		OHIP
Coronary angiogram		OHIP/CIHI-DAD
Coronary revascularization		OHIP/CIHI-DAD
Echocardiography		OHIP/CIHI-DAD
Holter monitoring		OHIP/CIHI-DAD

Other Variables		
Dialysate Temperature (baseline)		Case Report Forms**
Pre-dialysis systolic blood Pressure (baseline)		Case Report Forms**
Pre-dialysis diastolic blood pressure (baseline)		Case Report Forms**
Mean intra-dialytic nadir systolic blood pressure (baseline)		Case Report Forms**
Diastolic blood pressure accompanying the intra-dialytic nadir systolic blood pressure (baseline)		Case Report Forms**
Date of first nephrology visit		ORRS
Height		ORRS
Last measure weight		ORRS
Body Mass Index (BMI)		ORRS
History of Renal Transplant		ORRS /CIHI-DAD/OHIP
First Dialysis Modality		
Peritoneal Dialysis		ORRS/CORR
Hemodialysis		ORRS/CORR
Had a late nephrology referral		ORRS/CORR
Vascular access used at index date (April 01, 2017)		
Arteriovenous fistula		ORRS/CORR
Arteriovenous graft		ORRS/CORR
Central venous catheter		ORRS/CORR
Hemodialysis Characteristics at Index Date		
Patients Dialyzing in an Acute Care Hospital		ORRS
Patients Dialyzing in a Chronic or Community Hospital		ORRS
Duration of all dialysis modalities (Months)		ORRS
Centre Factors		
Number of patients at centre		ORRS
Centre Transplant Rate in previous 24 months		ORRS /CIHI-DAD/OHIP
Centre Death Rate in previous 24 months		ORRS/RPDB
Centre Transfer rate in previous 24 months		ORRS
Number of stations within centre		ORRS
Centre uses electronic dialysis run sheets		Case Report Forms**
Centre uses tympanic temperature measurement		Case Report Forms**
Centre uses heated chairs		Case Report Forms**

ODB= Ontario Drug Benefit database contains claims for prescription drugs received under the Ontario Drug Benefit program. Most are for those >=65 but from 1997 forward we also have data on other ODB program; OLIS=

Ontario Laboratories Information System; ORRS=Ontario Renal Reporting System has information is a database of all pre-dialysis, acute dialysis and chronic dialysis patients in Ontario since 2010; CIHI-DAD= Discharge Abstract Database records detailed diagnosis and procedural information on all hospitalizations in Ontario. Up to 25 unique diagnostic and 20 procedural codes can be assigned to each hospitalization.; OHIP= Ontario Health Insurance Plan database contains health claims for inpatient and outpatient physician services;

* Depression is defined as (1) having two events of OHIP diagnosis, hospitalizations, or ODB drug prescription; or (2) having at least one event in at least two of OHIP diagnosis, hospitalizations, or ODB drug prescription.[80]

**This information is captured on the dialysis run sheet that is completed with every dialysis treatment in Ontario (i.e. centres do not have to collect additional data outside standard of care).

++ History of components of primary or secondary outcomes

Appendix 8: Algorithm for capturing primary composite outcome

Outcome	Algorithm	Position of code	Performance
Cardiovascular-related death ~~Ѧ~~, ¥	ORGD: Leading Cause of Death LCD_33 = Chronic rheumatic heart disease LCD_34 = Hypertensive disease LCD_35 = Ischemic heart disease LCD_36 = Pulmonary heart disease and related LCD_37 = Nonrheumatic valve disorders LCD_38 = Cardiomyopathy LCD_39 = Cardiac arrest LCD_40 = Cardiac arrhythmias LCD_41 = Heart failure and complications, ill-defined heart disease LCD_42 = Cerebrovascular diseases LCD_43 = Atherosclerosis LCD_44 = Aortic aneurysm and dissection	N/A	Not available
Cardiovascular-related death	**ICD-10:** I00 - I78 AND Dischdisp="07" or death in Registered Persons Database during the hospital stay	Primary Diagnosis	RPDB has an accuracy of 99% for capturing death [81]
Hospital admission with ischemic stroke	***ICD-10:*** I63 (excl. I63.6), I64, H341	Primary Diagnosis	PPV= 85% [82,83]
Hospital admission with myocardial infarction	***ICD-10:*** I21, I22	Primary Diagnosis	Sn= 89%, PPV= 87% [84]
Hospital admission with heart failure	**ICD-10:** I50	Primary Diagnosis	Sn=61% , Sp=98%, PPV=66%[85]

Abbreviations: ICD = International Classification of Disease; OHIP = Ontario Health Insurance Plan; Dischdisp=Discharge disposition; Sn=Sensitivity; PPV= Positive Predictive Value; LCD=Leading Cause of Death; ORGD=Office of Registrar General – Deaths; RPDB = Registered Persons Database

~~Ѧ~~ Due to the time lag in data capture, deaths from ORGD will only capture events for the follow-up period between April 3rd, 2017 and December 31st, 2020. These events capture both in- and out-of-hospital cardiovascular-related deaths. For the remaining study period, we will only be able to capture in-hospital deaths using ICD-10 codes.

¥ Personal communication with Dr. Jack Tu who is part of a working group conducting a validation of this outcome using existing Ontario clinical trial data as the reference standard.

Appendix 9: Justification for using a composite primary endpoint

Our composite primary endpoint is composed of individual components that we believe will have a treatment effect in the same direction and magnitude and are clinically important – appreciating cardiovascular-related mortality is a more detrimental outcome than hospitalization. The outcome will provide an overall sense of the impact of the intervention on cardiovascular morbidity.

While there is some debate in the literature about including hospital admission with congestive heart failure as a component outcome of major cardiovascular events,[86] we chose to include it given that a personalized dialysate temperature may lead to fewer heart failure admissions if there is less cardiac ischemia or less left ventricular dysfunction over time. As well, patients who have a preserved blood pressure during dialysis may be less likely to stop their dialysis treatments early or may have more fluid removed on their dialysis treatments. In our analysis of historic Ontario data, the median stay for a hospital admission with congestive heart failure (ICD-10 code I50) in dialysis was 6 days (25th, 75th percentiles: 3, 10).

There is a strong relationship between intradialytic hypotension and myocardial stunning because of transient abnormalities in cardiac regional wall motion that occur in the presence of coronary hypoperfusion. Rapid reductions in blood pressure predispose to myocardial stunning because coronary flow is dependent on central arterial pressure. Hypotensive episodes also associate with aging of the arterial system, as well as extensive calcification and stiffening of the arterial walls.[87] The cumulative contribution of hypotensive events to cardiovascular events have been significant.[11,13,53] Reduction of dialysate temperature is one technique that has been shown to be effective in decreasing the of risk intradialytic hypotensive events and stabilizing blood pressure, reducing injury to the heart and brain as seen in magnetic imaging studies.[9]

In observational studies, compared to patients that did not experience intradialytic hypotension, patients that experienced intradialytic hypotension in more than 10% of their hemodialysis treatments had a hazard ratio of 1.22 (95% CI: 1.02 to 1.48) for cardiovascular-related mortality, 1.20 (95% CI: 1.00 to 1.45) for hospitalizations of non-fatal myocardial infarction, and 1.22 (95% CI: 1.11 to 1.34) for hospitalizations with heart failure or volume overload.[44] Similarly, compared to patients that did not experience intradialytic hypotension, those that experienced intradialytic hypotension in more than 10% of their treatments had a 1.23 (95% CI: 1.08 to 1.41) risk of experiencing a major cardiovascular event (defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular-related mortality).[44] The study did not specifically provide the risk of experiencing an ischemic stroke.

The historic annual hazard rate of the components of the primary outcome in our data sources have similar baseline annual event rates: 0.031 for cardiovascular-related mortality, 0.030 for hospital admission with myocardial infarction, 0.032 for hospital admission with congestive heart failure, and 0.012 for hospital admission with ischemic stroke per person-year.

Appendix 10: Other important outcomes

Lower limb amputation: Patients on hemodialysis, especially those with diabetes, have a high hazard rate of amputation. The historic baseline hazard rate of lower extremity amputations over a 4-year period (from April 1, 2013 to March 31, 2017) for an open cohort was 0.026 events per person-year. For patients with diabetes, this historic hazard is 0.039 events per person-year. Amputations are associated with cardiovascular risk factors and likely linked to vascular injury caused by hemodialysis-induced ischemia, which complicates pre-existing arterial disease and diabetes related injury.

Major falls and fractures: Many patients on dialysis are frail and prone to falling, which may also predispose them to suffer a fracture. Bone fractures are an important outcome and can result in morbidity, high economic costs, and mortality. The three-year incidence of falls requiring a hospitalization ranges from 3% to 12% for patients on dialysis, with elderly females being the highest risk.[88] Major fractures (hip, forearm, pelvis, or proximal humerus) are also common occurring in nearly 6% of patients each year.[88] In our cohort, the historic hazard rate of major fractures over a 4-year period (from April 1, 2013 to March 31, 2017) for an open cohort was 0.037 events per person-year. Intra-dialytic hypotension might increase the rate and severity of falls after a hemodialysis session leading to additional fractures requiring hospitalizations.

Emergency department visits or hospitalizations (analyzed separately and as a composite): Patients on hemodialysis are frequently hospitalized and account for 5% to 7% of healthcare expenditures in developed countries despite comprising a very small percentage of the general adult population.[89–92] These patients have several characteristics that make them vulnerable to hospitalization and emergency department use, including multimorbidity, high rates cardiovascular complications, and complex

medication regimens. The historic hazard rate for emergency department visits was 1.05, all-cause hospitalizations was 0.65, and the composite all-cause emergency department visits or hospitalizations over a 4-year period (from April 1, 2013 to March 31, 2017) was 1.22 events per person-year.

Intradialytic hypotension:

In general, there is no consensus, evidence-based, medical definition for intradialytic hypotensive episodes.[93,94] Most definitions of intradialytic hypotension are made up of two or more components: 1) an absolute or relative decline in the intradialytic systolic blood pressure from the pre-dialysis systolic blood pressure reading; and 2) a nadir systolic blood pressure reading below a specific threshold.[94] Some definitions include an additional component of intradialytic symptoms (e.g., cramping, yawning,) and/or the need for an intradialytic intervention (e.g., Trendelenburg position, fluid administration,). In our trial, we will not have information on patient symptoms of hypotension or interventions used to treat these episodes. It has been previously shown that adding symptom or intervention criteria to intradialytic hypotension definitions did not change the strength of association with mortality.[10]

In MyTEMP, in post-hoc analysis, we will define intradialytic hypotension if the patient experiences any of the following: **i)** nadir systolic blood pressure < 90 mmHg anytime during the hemodialysis session (regardless if patients begin the hemodialysis session with systolic blood pressure below 90 mmHg); or **ii)** drop in systolic blood pressure by ≥ 30 mmHg from the pre-dialysis systolic blood pressure reading.[95,96] We will also consider alternate definitions of intradialytic hypotension:

a) Systolic blood pressure < 90 mmHg alone. A nadir systolic blood pressure of < 90 mmHg was strongly associated with all-cause mortality in a previous observational study.[10,94]

b) At least a 25% relative reduction in nadir systolic blood pressure from pre-dialysis systolic blood pressure or nadir ≤ 90 mmHg.[53,94,97]

c) At least a 25% relative reduction in nadir systolic blood pressure from pre-dialysis systolic blood pressure.[53,94,97]

d) A drop in nadir systolic blood pressure by ≥ 35 mmHg from pre-dialysis systolic blood pressure.[94,98]

Appendix 11a: Statistical power estimates for different hazard ratios of the treatment effect different coefficients of variation, and different rates of the primary composite outcome. A statistical power estimate of 0.8 means the trial has 80% power to detect the specified hazard ratio with the intervention vs. control, if the effect in truth exists.

Different Hazard Ratios of the Treatment Effect	Different rates of the primary composite outcome (per person-year)			
	0.08	**0.09**	**0.1**	**0.11**
CV=0.19				
0.75	95%	96%	97%	98%
0.8	80%	83%	85%	88%
0.85	53%	56%	59%	62%
0.9	25%	27%	29%	31%
CV=0.20				
0.75	94%	96%	97%	97%
0.8	78%	82%	84%	86%
0.85	52%	55%	58%	60%
0.9	25%	26%	28%	30%
CV=0.21				
0.75	93%	95%	96%	97%
0.8	77%	80%	83%	85%
0.85	50%	53%	56%	59%
0.9	24%	26%	27%	28%
CV=0.22				
0.75	93%	94%	95%	96%
0.8	76%	79%	81%	83%
0.85	49%	52%	54%	57%
0.9	23%	25%	26%	27%
CV=0.23				
0.75	92%	93%	95%	96%
0.8	74%	77%	80%	82%
0.85	47%	50%	53%	55%
0.9	23%	24%	25%	27%
CV=0.24				
0.75	91%	93%	94%	95%
0.8	73%	76%	78%	80%
0.85	46%	49%	51%	53%
0.9	22%	23%	24%	26%

CV=0.25				
0.75	90%	92%	93%	94%
0.8	71%	74%	76%	79%
0.85	45%	47%	50%	52%
0.9	21%	23%	24%	25%

CV = Coefficient of variation. We assumed a total follow-up of 4 years, a cluster harmonic average of 163 person-years, alpha of 0.04, and 42 clusters per arm. Starred values (*)highlights conditions where we have at least 80% power to detect a difference, if a difference truly exists.

Appendix 11b: Details of power estimates using computer simulations.

In addition to the closed form sample size estimation, we also confirmed our power calculations using simulation studies. This method allowed us to account for the complexity of our study design, variable cluster (HD centre) sizes, different follow-up periods among patients in participating centres, clustering, and censoring events during follow-up.[99–102] We generated 1000 simulated data sets based on the correlation structure observed for the prevalent HD cohort from April 1st, 2013 to March 31st, 2017. For each simulated dataset, 84 observations (i.e., HD centres) were generated and included information on the following: 1) number of outcome events that occurred within a 4-year period, 2) number of days of follow-up, and 3) a randomly allocated indicator representing the control or intervention arm. Assuming a two-tailed alpha 0.04, we have 56%, 81%, and 96% power to detect a 15%, 20%, and 25% hazard rate reduction in the primary composite endpoint, respectively.

Appendix 11c: Power estimates for the key secondary endpoint of between group difference in the mean drop of systolic blood pressure (mmHg).

	Standard deviation of the cluster-period means				
Between group difference (mmHg)**	**2**	**4**	**5**	**6**	**7**
1	54%	16%	12%	6%	5%
2	100%	71%	57%	31%	22%
3	100%	98%	94%	71%	55%
4	100%	100%	100%	94%	85%
5	100%	100%	100%	100%	97%
6	100%	100%	100%	100%	100%
7	100%	100%	100%	100%	100%
8	100%	100%	100%	100%	100%
9	100%	100%	100%	100%	100%
10	100%	100%	100%	100%	100%

**Between-group difference in the mean drop of systolic blood pressure.

The above data assumed there are 84 clusters with at least 6 repeated observations and a constant intraclass correlation coefficient (ICC) of 0.4 and an average drop across all sites/periods of 28 mmHg with an alpha of 0.01.

Shaded area highlights conditions where we have at least 80% power to detect a difference, if a difference truly exists.

Appendix 12: Bayesian analysis

As a first step, we will use a minimally informative reference prior (which regards all possible log-hazard ratio values to be equally likely and will produce results largely dependent on observed data from MyTEMP). Sources of prior information will include: 1) results from published literature that compare temperature-reduced hemodialysis to standard hemodialysis temperature;[66–68] and 2) historic data from our administrative data sources. At the analytic stage, we will update **Table 3** based on current data from the literature.

We will use PROC PHREG (SAS 9.4, NC Cary) – in a similar manner as conducted for the primary analysis – and invoke the BAYES statement to request that the parameters of the model be estimated by using Gibbs sampling techniques.[103] This approach enables the specification of prior information, control the sampling, as well as obtain posterior summary statistics and convergence diagnostics. Convergence of the generated Markov chain will be assessed by examining the trace plot, autocorrelation function plot, and posterior density plot.

Appendix 13: Planned additional analyses

We will conduct several analyses to assess the robustness of the results from the primary analysis. These additional analyses will include:

1. Adjusted Cox model to test the effect of the intervention vs. control on the primary composite outcome.

2. Treating kidney transplants, switching to a home dialysis modality, and switching to a non-participating hemodialysis centre as a censoring event.

3. Assuming a closed cohort, where we will include only a subset of our cohort who were on hemodialysis prior to April 3rd, 2017. Using historic data, we estimate there will be ~7500 patients included in this cohort.

4. In our historic data, over a 4-year follow-up period we found 19% of patients experienced at least one event in our primary composite outcome and 4% of all patients had more than one event. Given the infrequent number of recurrent events, we decided to use a parsimonious approach of time-to-first event model for the primary analysis. However, it will be important to understand repeated events (i.e. one patient may contribute multiple events) that may occur during the study period.

   At first, we will explore these repeated events descriptively to estimate differences across the two arms. We will also conduct a Cox regression analysis that accounts for multiple events per patient. We will define a hospitalization episode of care as either a direct admission to an acute care hospital from which the patient is subsequently discharged home, or a continuous sequence of hospitalizations (i.e., a hospital discharge and admission within the same day is

considered to all be part of the same episode of care). Unless the same event is within the episode of care, patients can contribute multiple events from the time they enter the study and until a censoring event.

5. Patients on hemodialysis are at high risk of non-cardiovascular causes of death (e.g., sepsis, malignancy), may receive a kidney transplant, or switch to home dialysis. The extent to which these events impact the probability of observing the event of interest can be explored through competing risks. Ideally, we will see comparable results with the Cox model, however in absence of agreement, we will assume that the bias of results in the Cox model occurs due to the number, type, and distribution of competing events. In this analysis, we will censor follow-up when patients switch to another centre not in the same group allocation.

6. For the as-treated analysis, patients will be coded as receiving the intervention depending on the centre where they are being treated. For patients that experience an outcome of interest within 30-days of switching to another centre, the outcome will be attributed to the previous centre.

Appendix 14: Main responsibilities of the data safety monitoring board

1. Consider factors external to this trial when relevant information becomes available. This includes any scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of this trial.
2. Review the conduct of the trial, including protocol violations.
3. Review data on hemodialysis centre recruitment, accrual, and retention, as well as assessments of data quality, completeness, and timeliness.
4. Protect the confidentiality of the trial data and the DSMB discussions.
5. Approve the statistical analysis plan prior to trial analysis.
6. Make recommendations to continue, modify, or stop the trial if necessary.

To date, with the information available about the safety of temperature-reduced dialysis, the DSMB is not planning to perform any between-group interim analyses during the trial period.

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